



Original Article

Patient-centered Outcomes in Breast Cancer: Description of EQ-5D-5L and EORTC-QLQ-BR23 Measurements in Real-world Data and Their Association With Survival

M.R. Monteiro, N.C.C. Nunes, J. Crespo, A.B.K. Abrahão, G. Buscacio, L.C.C. Lerner, L. Sermoud, R. Arakelian, G. Piotto, C. Lemos, R. Campos, D. Victorino, P.M. Andrade, T.A.V. Ferreira, J.P. Pecoraro, F. Meton, M.F. Gai, L.H. Araujo

COI Institute, Clinical Research Department, Americas Oncology Cancer Center, São Paulo, Brazil

Abstract

Aims: In recent years, major improvements in breast cancer treatments have led to a significant increase in survival. Despite that, this population's quality of life (QoL) information is lacking, especially real-world data.

Materials and methods: This was a prospective, multicentre, observational study of female breast cancer patients, without prior systemic treatment, treated between 2012 and 2019 in private health care in Brazil. QoL was assessed by two questionnaires, the EQ-5D-5L and the EORTC-QLQ-BR23. Additional data were retrospectively collected.

Results: The study comprised 1372 patients, most with early-stage disease (80.2% stages 0–II). At a median follow-up of 25.6 months, the estimated 3-year overall survival was 93.6%. Patients with locally advanced and metastatic breast cancer had the lowest visual analogue scale scores and the highest symptom burden in all dimensions of EQ-5D-5L, but with the most significant improvement after treatment. With the EORTC-QLQ-BR23 questionnaire, patients undergoing lumpectomy had a better perception of body image. Axillary dissection led to greater arm symptoms after 12 months, radiotherapy enhanced breast symptoms and patients treated with chemotherapy had significant worsening in the effects of systemic therapy compared with endocrine or HER2 therapy. Staging and immunohistochemical subtype correlated with survival and with several QoL parameters, but overall survival was not independently affected by patient-reported outcomes in this cohort.

Conclusion: Our results show that early diagnosis and access to treatments with fewer side-effects, such as endocrine or targeted therapy, and less aggressive surgeries are the best strategies to achieve a better QoL for breast cancer patients.

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Key words: Breast cancer; EORTC-QLQ-BR23; EQ-5D-5L; patient-reported outcomes; quality of life

Introduction

Breast cancer is the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases/year (11.7% of total cases) [1]. It is the leading cause of cancer mortality in the female population in Brazil, comprising 16.1% of total cancer deaths [2,3]. The overall rates of breast cancer incidence and mortality have been continuously increasing, with differences according to geographical location and age [1,4,5]. In recent years, major improvements in

breast cancer treatments have led to a significant increase in survival, both at early and advanced stages [6,7]. However, a large number of patients will experience short- and long-term side-effects of these treatments [7]. The impact on physical and mental health has several potential issues that may affect a patient's quality of life (QoL), including financial and psychological distress, impairment in treatment, sexual and fertility problems, among others [8–10]. In this perspective, improving QoL must be equally prioritised by the oncologist, as it is to cure more patients with early stage breast cancer and improve survival for advanced disease.

Furthermore, when analysing patient-reported outcomes, one must consider that different cultures, needs and issues of each population in different countries might impact their QoL. Brazil is a country that faces many social

Author for correspondence: M. Monteiro, COI Institute, Clinical Research Department, Americas Oncology Cancer Center, Maestro Cardim Street 343/11, Liberdade, São Paulo, SP 01323-000, Brazil.

E-mail address: marianarmonteiro@hotmail.com (M.R. Monteiro).

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disparities, which can be reflected in the setting where patients undergo treatment – public or private healthcare system – and the region where the cancer center is located [11]. QoL encompasses cognitive, physical, emotional, social, sexual, spiritual and other domains of patients' perspective, which are influenced by particular individual experiences, beliefs, expectations and perceptions [10]. Although different tools have been used to assess QoL, the best tool has not been fully established [12–14].

In recent decades, the concept of value-based medicine has emerged as a tool to measure outcomes [12,14]. In addition to improvements in survival, reductions in toxicities and better QoL have become an interesting strategy for inclusion in healthcare cost and reimbursement calculations [15]. To harmonise efforts around the globe, the International Consortium for Health Outcomes Measurement (ICHOM) has defined standard sets to serve as a guide for aligning outcome measurement initiatives internationally [16,17]. In line with the ICHOM group, Instituto COI – a research-focused non-profit organisation – in partnership with Americas Oncologia, has conducted prospective registries with focus on collecting patient-centred outcomes. In 2018, we reported the clinical characteristics and survival outcomes from the first patients included in this trial [18]. The current report provides patient-centered outcomes and updated survival data on breast cancer patients treated at Americas Oncologia (a private healthcare institution) facilities located in the Brazilian states of São Paulo and Rio de Janeiro.

Materials and Methods

Study Design

We conducted a multicentre, prospective and observational study of female patients with breast cancer treated in private health care, in two Brazilian states, Rio de Janeiro and São Paulo, diagnosed between April 2012 and November 2019. Eligible patients were 18 years or older, had histologically or cytologically confirmed invasive or *in situ* breast cancer and had not received prior systemic treatment or radiotherapy. Patients had to be treated and monitored at our institution. Exclusion criteria were male gender, insufficient data for analysis or patient refusal. Patients were included regardless of disease stage or Eastern Cooperative Oncology Group (ECOG) status. All patients provided oral and written informed consent. The study was approved by a local Ethics Committee.

QoL was assessed at baseline and every 3 months in the first 2 years, and then every 6 months until 5 years of follow-up, with two different questionnaires: the EQ-5D-5L and the EORTC-QLQ-BR23. The EQ-5D-5L is a questionnaire that describes patient's perception of health, regardless of the type of disease, and consists of two components: a descriptive system and a visual analogue scale (EQ-VAS). The descriptive system comprises five dimensions: mobility, self-

care, usual activities, pain/discomfort and anxiety/depression, each response with five levels of severity. EQ-VAS is a numerical scale with scores from 0 to 100 that measures general health status from the patient's own perception [19]. The EORTC-QLQ-BR23 comprises 23 questions to assess important factors in breast cancer survivors. These include four functional scales and four symptom scales. High scores on functional scales represent better functioning; high scores on symptom scales show higher issues. The functional scale includes perception of a 'body image', 'sexual functioning', 'sexual enjoyment' and 'future perspective'. The symptom scale includes 'systemic therapy side-effects', 'upset by hair loss', 'breast symptoms' and 'arm symptoms' [20].

Additional data were retrospectively collected through electronic medical records, regarding demographic variables, ECOG performance status, staging, histological subtype and type of treatment. These variables were used to stratify risk factors and calculate survival.

Statistical Methods

Baseline characteristics were described through continuous or categorical variables. Continuous variables were described using means and standard deviations, or medians and interquartile ranges. Categorical variables were described using absolute or relative frequencies. Overall survival was estimated using the Kaplan–Meier method, defined as the time from the study inclusion until death by any cause. For patients who were alive or lost to follow-up on the trial cut-off date, data were censored at the time of the last contact. The two main prognostic covariates were staging and histological subtype. We used the Log-rank model to compare survival according to covariates. For significant values, we considered $P < 0.05$. A Cox model was used to assess the risk ratio of death and 95% confidence intervals and P values were also presented.

Questionnaire scales or items were scored according to EORTC published algorithms [19,20]. For each scale or item, a linear transformation was applied to standardise the raw score to a range of 0–100. The five dimensions of the EQ-5D-5L and the categories of the EORTC-QLQ-BR23 questionnaire were described according to staging and subtypes, with a presentation of absolute and relative frequencies. For the Likert scale, we present the means and compare their distribution in each of the strata levels using the Kruskal–Wallis test. In the EQ-5D-5L questionnaire, the scores were also categorized, considering values greater than two. In this case, we used Fisher's test to compare distributions according to strata. All dimensions were evaluated over time using means and standard deviations. A linear mixed model was used, with the scores as a dependent variable to assess the changes over time. Results were reported as increments relative to the baseline category, using 95% confidence intervals and P values.

Analyses were carried out using the R v 4.1.0 software (R Core Team, 2021). For the hypothesis tests, a significance level of 5% was considered.

Results

From April 2012 to November 2019, 7964 patients were diagnosed with breast cancer at Americas Oncologia centres. More than 6000 patients were screened but failed to meet the eligibility criteria and were excluded. Finally, 1372 patients were included in the study (see [Supplementary Figure S1](#)). The EQ-5D-5L and the EORTC-QLQ-BR23 questionnaires were answered by 1367, 1334, 1294, 1247, 1182 and 957 patients at baseline, 3, 6, 9, 12 and 24 months, respectively. The withdrawal of consent and patient's refusal to answer were the main causes for incomplete questionnaires.

Baseline Characteristics and Overall Survival

Baseline characteristics are summarised in [Table 1](#). In total, 1372 patients were included in the final study. The median age at diagnosis was 53.8 years and 60.7% were postmenopausal. Most patients had breast surgery (93.7%).

Table 1
Demographic and clinical baseline characteristics

Variables	n = 1372
Median age at diagnosis (years)	53.8 ± 12.6
Menopausal status	
Pre-/perimenopausal	536/1372 (39.1%)
Postmenopausal	827/1372 (60.3%)
Missing	9/1372 (0.6%)
Type of breast surgery	
Lumpectomy	828/1286 (64.4%)
Mastectomy	468/1286 (35.6%)
Type of axillary surgery	
ALND	440/1180 (37.3%)
SLNB	740/1180 (62.7%)
SLNB followed by ALND	222/1180 (18.8%)
Histological subtype	
<i>In situ</i> carcinoma	157/1372 (11.4%)
Invasive breast cancer	1211/1372 (88.3%)
Missing	4/1372 (0.3%)
HR/HER2 status	
HR+/HER2–	836/1372 (60.9%)
HR+/HER2+	169/1372 (12.3%)
HR–/HER2+	67/1372 (4.9%)
HR–/HER2– (triple negative)	157/1372 (11.4%)
Missing	143/1372 (10.4%)
Staging	
0	157/1372 (11.4%)
I	504/1372 (36.7%)
II	437/1372 (31.8%)
III	225/1372 (16.4%)
IV	45/1372 (3.3%)
Missing	4/1372 (0.3%)
Systemic treatment	
Chemotherapy	842/1372 (61.4%)
Endocrine therapy	974/1372 (71.0%)
HER2 target therapy	218/1372 (15.9%)
Radiotherapy	953/1372 (69.5%)

ALND, axillary lymph node dissection; HR, hormone receptor; SLNB, sentinel lymph node biopsy alone.

The most common type of surgery was lumpectomy (64.4%) and surgical axillary evaluation (86%), in which approximately one-third were submitted to axillary lymph node dissection (ALND). In this cohort, we observed patients predominantly with early stage (80.2% stages 0, I or II) disease.

At a median follow-up of 25.6 months, 67 deaths were reported. The estimated 3-year overall survival was 93.6% (95% confidence interval 91.7–95.4%) ([Figure 1A](#)). However, the risk of death was higher among patients with advanced stages ([Figure 1B](#)) and hormone receptor-negative (HR–) disease ([Figure 1C](#); $P < 0.001$). Overall survival was significantly higher among patients with stages I and II (3-year overall survival 98.4% and 95%, respectively), compared with stages III and IV (3-year overall survival 83.9% and 60.9%, respectively). In the HR+/HER2– subtype group, patients with luminal B disease had numerically inferior survival compared with luminal A subtypes, but without statistical significance ([Figure 1D](#)).

Health-related Quality of Life at Baseline

Among the five dimensions of the EQ-5D-5L questionnaire, most patients reported no problems at baseline (score 1); however, anxiety/depression were reported as slight (score 2) or moderate problems (score 3) in 37.1% and 19.5% of the cases, respectively. Among the EQ-VAS scale, a patient's perception of health was significantly worse at a more advanced stage (see [Supplementary Table S1](#)). Patients with locally advanced and metastatic breast cancer had higher scores on all dimensions of EQ-5D-5L, including higher problems with mobility ($P < 0.001$), pain/discomfort ($P < 0.001$), usual activities ($P < 0.001$), anxiety/depression ($P = 0.004$) and impact on self-care ($P = 0.002$) ([Figure 2A](#) and [Supplementary Table S2](#)). In the analysis of baseline QoL according to breast cancer subtypes, the distributions were quite similar across all parameters. Patients with triple-negative tumours had a slight impact on self-care ($P = 0.005$), whereas HR–/HER2+ patients had numerically worse scores in pain/discomfort ($P = 0.262$) and anxiety/depression ($P = 0.132$), without reaching statistical significance ([Figure 2B](#) and [Supplementary Tables S3 and S4](#)). Baseline EQ-5D-5L questionnaire dimension scores did not correlate with overall survival in this population.

The baseline EORTC-QLQ-BR23 questionnaire was reported as functional and symptom scales. In our cohort, patients had similar results compared with the EORTC reference values manual [21], except for higher scores of sexual functioning and lower scores of sexual enjoyment ([Table 2](#)). Analysing the EORTC-QLQ-BR23 scores according to staging, stage IV patients had worse scores for systemic therapy-related symptoms (for example, dry mouth, feeling ill or hot flashes), but better scores for sexual function compared with other stages. Stage III patients were the group with the highest scores for breast symptoms and stage 0/I patients had the highest self-perspective of the future (see [Supplementary Figure S2A, S2B, Table S5](#)). According to HR/HER2 status, the proportions of baseline

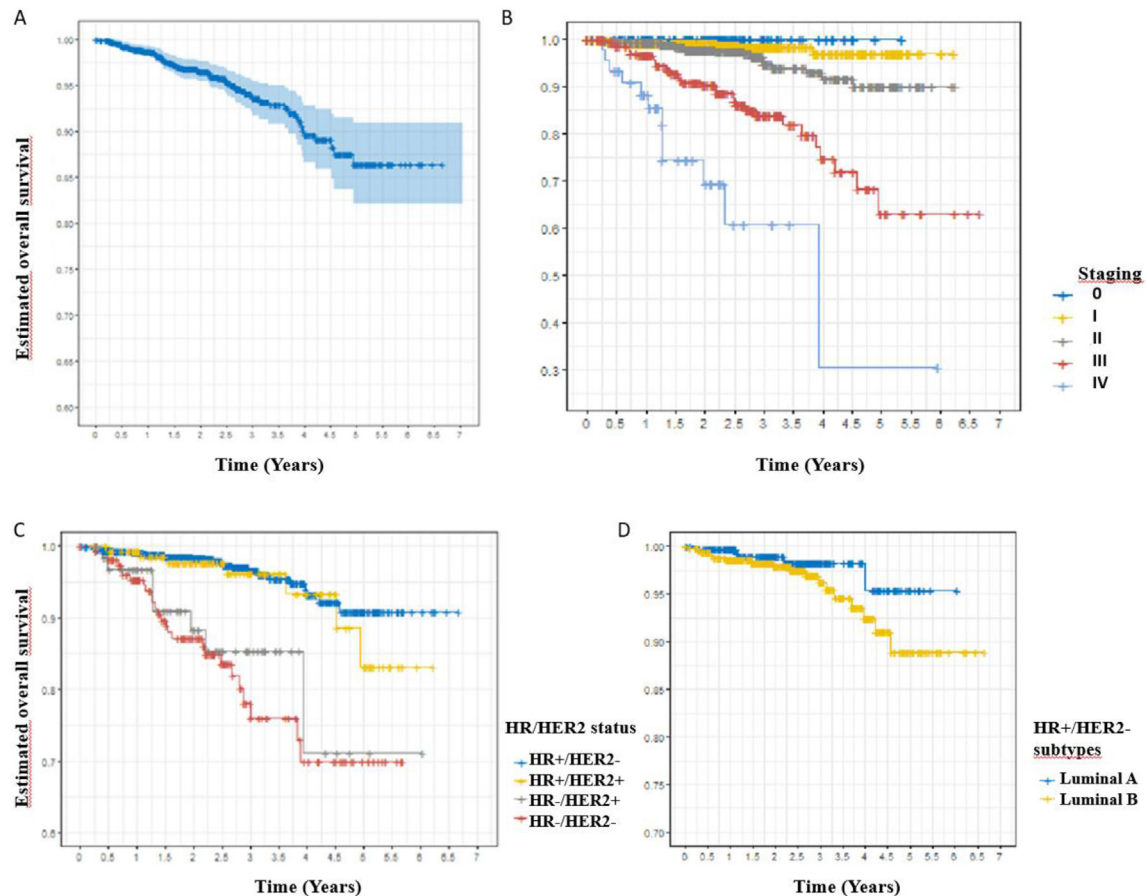


Fig 1. Cox proportional hazard survival curves of overall survival on (A) the total population, (B) by staging and (C, D) by hormone receptor/human epidermal growth factor receptor (HR/HER2) status. (A) The estimated 2-, 4- and 5-year overall survival in the total population was 96%, 90% and 86.4%, respectively. (B) The 5-year overall survival was 97%, 90%, 63.1% and 30.5% for stages I, II, III and IV, respectively. Compared with stages 0 and I, the relative risk for death was 3.28 ($P = 0.013$), 13.78 ($P < 0.001$) and 44.51 ($P < 0.001$) times higher for stages II, III and IV, respectively. (C) Compared with HR+/HER2- subtype, the relative risk for death was 1.39 ($P = 0.44$), 4.68 ($P = 0.0002$) and 5.84 ($P < 0.001$) times higher for HR+/HER2+, HR-/HER2+ and HR-/HER2- subtypes, respectively. (D) Luminal B subtype patients had inferior survival, without reaching statistical significance. Values of $P < 0.05$ were considered statistically significant.

measures were similar across all subtypes (see [Supplementary Figure S2C, S2D, Table S6](#)). Similarly, baseline EORTC-QLQ-BR23 measures did not correlate with overall survival in this population.

Comparisons of Quality of Life Parameters Over Time

According to EQ-VAS ([Figure 3](#)), in our cohort there was no clinically significant difference in QoL over time. Numerically, lower scores were observed at 3 months, but with a trend towards long-term improvement (see [Supplementary Table S7](#)). However, for stage IV patients, who had the lowest baseline scores, there was a significant improvement in QoL 9 ($P = 0.01$) and 12 months ($P = 0.005$) after the initial treatment (see [Supplementary Table S8](#)). According to HR/HER2 status, triple-negative tumour patients had a significant worsening of their perception of QoL in the first 3 ($P = 0.01$) and 6 months ($P = 0.002$), which numerically recovered and became superior than baseline after 9 months of treatment, although without statistical significance ($P = 0.85$). Patients with HER2-positive breast

cancer were those with the best long-term EQ-VAS score at 12 months ($P = 0.03$) (see [Supplementary Table S9](#)).

The EORTC-QLQ-BR23 questionnaire scales were evaluated in the total cohort. Changes from baseline parameters as well as a statistically significant effect over time were adjusted by staging (see [Supplementary Table S10](#)). In the first 6 months of the initial treatment, patients had worse body image and systemic therapy symptoms scores, but they had an improvement in sexual functioning and enjoyment over time ($P < 0.0001$). Breast and arm symptoms remained stable, and future perspective reached the best parameters after 12 months (see [Supplementary Figure S3](#)). When symptoms were analysed over time according to the treatment performed ([Figure 4](#)), patients undergoing lumpectomy had a better perception of body image, although breast and arm symptoms remained similar compared with mastectomy. Patients who underwent ALND maintained similar and stable breast symptoms, but had worse arm symptom scores after 12 months of initial treatment, when compared with patients without axillary dissection. Patients who underwent chemotherapy

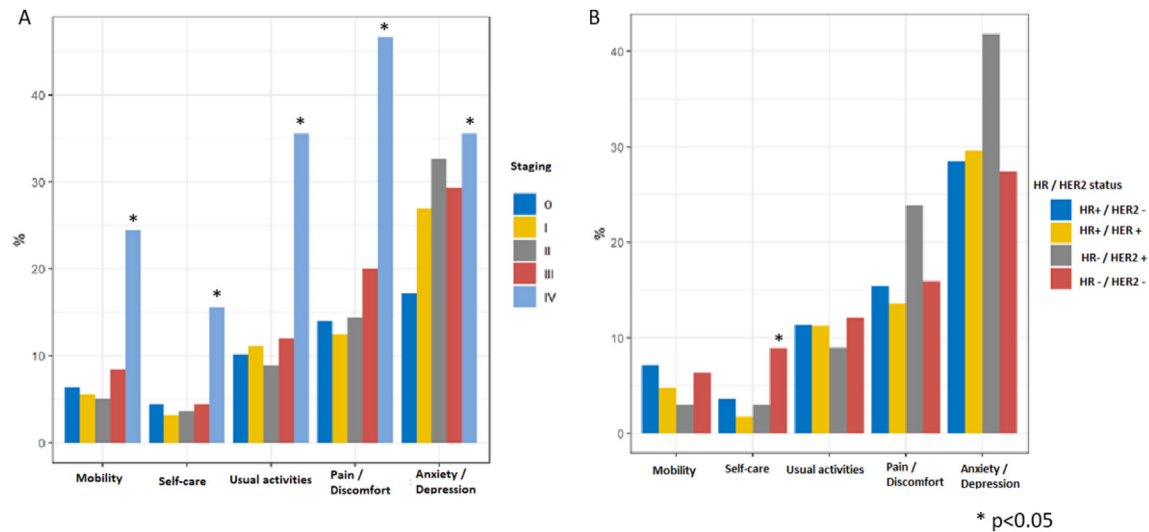


Fig 2. Distribution of categories of baseline variables of EQ-5D-5L > 2, according to (A) staging and (B) hormone receptor/human epidermal growth factor receptor (HR/HER2) status. The proportion of patients who answered 3, 4 or 5 (moderate symptoms, severe symptoms or 'unable to', respectively) on the EQ-5D-5L scale, according to stage and histological subtype. (A) Stage IV patients reported at least moderate symptoms in 24.4%, 15.6%, 35.6%, 46.7% and 35.6% in the categories mobility, self-care, usual activities, pain/discomfort and anxiety/depression, respectively, which was statistically higher compared with the other stages ($P < 0.05$). (B) Overall, no clinically relevant differences were found between the different histological types (HR/HER2 status) at baseline. Values of $P < 0.05$ were considered statistically significant.

showed a significant worsening of systemic therapy effects after 3–6 months of treatment when compared with no chemotherapy. On the other hand, patients treated with endocrine therapy did not show significant differences in systemic effects compared with those who were not exposed to endocrine therapy. Patients treated with HER2-targeted therapy had a slight increase in systemic therapy effects in the first 3 months. Herein it is worth mentioning that the chemotherapy backbone was not evaluated. Finally, patients who underwent radiotherapy scored higher for breast symptoms after 9 months compared with patients who did not receive radiotherapy (Figure 4).

Discussion

QoL is one of the main goals of cancer treatment. However, real-world data are lacking in the literature. To the best of our knowledge, this is the largest report on the real-world QoL of breast cancer patients in Latin America. However, it is important to highlight that our cohort may not represent a high proportion of the Brazilian population, who relies exclusively on the public healthcare system, whereas our study included only patients treated in a private healthcare system. The AMAZONA study described a large cohort of breast cancer patients in Brazil, 80.8% of whom were treated in the public system, and showed a higher proportion of patients undergoing mastectomy and adjuvant chemotherapy compared with our sample; the QoL was not measured in this study [11].

The reference values published in a manual in 2008 by the EORTC group remain the main source for comparison in clinical trials, and were used in the present study, although this manual has several limitations. For example, new

Table 2

EORTC-QLQ-BR23 constructed scales comparing the total population cohort with EORTC reference values

Variables	Mean (SD) of the total population (n = 1368)	Mean (SD) of the EORTC reference values (n = 2782) [21]
Functional scales		
Body image	85.5 (21.6)	80.5 (24)
Sexual functioning	66.1 (28.9)	20.7 (22.6)
Sexual enjoyment	32.8 (32.7)	51.9 (26.8)
Future perspective	40.2 (37.7)	49.4 (31.8)
Symptoms scales		
Systemic therapy	12.0 (14.7)	16.0 (12.0)
Breast symptoms	24.7 (24.3)	17.1 (17.2)
Arm symptoms	21.6 (24.3)	21.1 (22.2)

EORTC, European Organization for Research and Treatment of Cancer; SD, standard deviation.

treatments that can improve the QoL could be missing in outdated manuals [21,22].

Many studies were designed to correlate health-related QoL to survival [23–25]. The EORTC-QLQ-C30 was the most frequently used in studies, often supplemented by the EORTC-QLQ-BR23. A meta-analysis of EORTC trials showed that some measurements of the EORTC-QLQ-C30 questionnaire can predict mortality, regardless of clinical parameters [23]. Recently, Araujo *et al.* [25] showed that the degree of fatigue measured in the EORTC-QLQ-30 questionnaire was an independent factor of mortality in lung cancer patients. In our cohort, overall survival was consistent with our prior report [18], which can be explained by the high incidence of early-stage disease (I

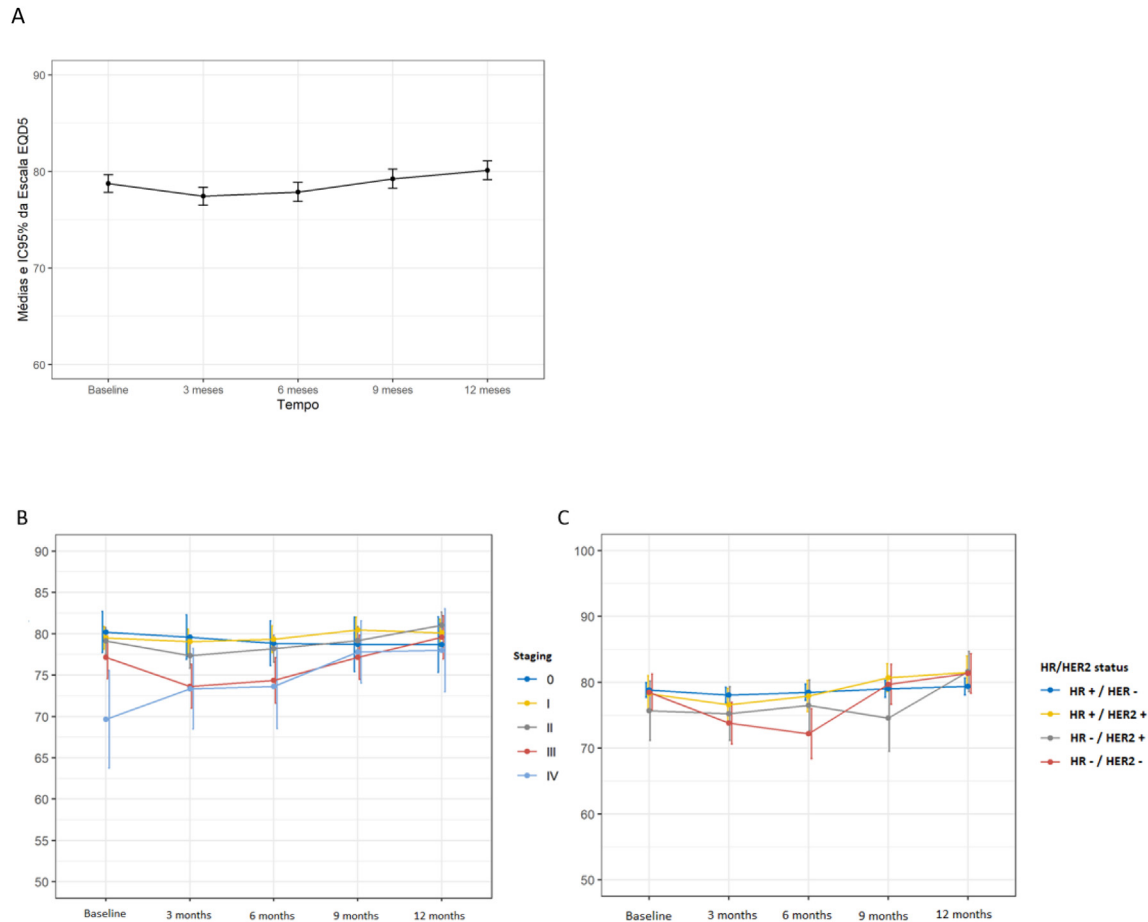


Fig 3. Means and 95% confidence interval of the EuroQoL visual analogue scale (EQ-VAS) in (A) the total population, (B) by stage and (C) by hormone receptor/human epidermal growth factor receptor (HR/HER2) status. The mean score on the EQ-VAS of the EQ-5D-5L questionnaire at baseline, 3, 6, 9 and 12 months, divided by stage and histological subtype (HR/HER2 status). (A) In the total cohort, there was a statistically significant decrease of 1.25 points from baseline at 3 months, and a recovery in up to 12 months, but without clinical relevance. (B) Patients with stage IV had a mean score of 69.66 at baseline and reached 78 mean score at 12 months, with the most relevant increase over time ($P = 0.005$). (C) According to HR/HER2 status, the most relevant differences were for patients with HR-/HER2+ subtype, who achieved an increase of 5.99 points in the mean score at 12 months compared with baseline ($P = 0.03$), and patients with HR-/HER- subtype (triple negative), which decreased by 5.74 points in 6 months compared with baseline ($P = 0.002$). Values of $P < 0.05$ were considered statistically significant.

and II) and the optimal treatment delivered in private health care. QoL measurements have not affected survival in our study, probably due to the low number of events in a cohort with good prognosis. Furthermore, unlike the EORTC-QLQ-C30 questionnaire, the EORTC-QLQ-BR23 describes symptoms reported by the patients but does not reflect the global health status. A new proposal for the EORTC-QLQ-BR23 questionnaire has been studied, including 45 questions to provide a more accurate and comprehensive assessment of the impact of newer treatments [26]. The main limitation of our study was the lack of the EORTC-QLQ-C30 questionnaire. However, at the time of study design, the aim was to assess specific symptoms of breast cancer and cost-effectiveness. This is an ongoing study, and a protocol amendment has been made to include this questionnaire [17].

Despite being a real-world study, it was possible to observe a high compliance rate in the adherence to questionnaires in the first year of follow-up. As most patients

completed their curative treatment within 1 year of diagnosis, QoL questionnaires beyond 12 months were not reported. As it represents a systemic treatment-naïve population, who have had undergone surgery before inclusion in the study, the baseline parameters of the EQ-5D-5L questionnaire showed slight or no symptoms, except for patients with advanced disease, who experienced a higher symptom burden. As expected, the diagnosis of breast cancer caused major psychological impacts on women's lives, which is compatible with higher scores in anxiety/depression. A higher score for pain/discomfort and anxiety/depression were also found in a Brazilian cohort, which included 196 treatment-naïve patients, mostly with advanced stages, treated in a public health system [27]. The EORTC-QLQ-BR23 questionnaire also represents a treatment-naïve population and we found higher scores in sexual functioning compared with the EORTC reference values. Lower sexual enjoyment scores can be explained by different population perceptions or by prior breast surgery.

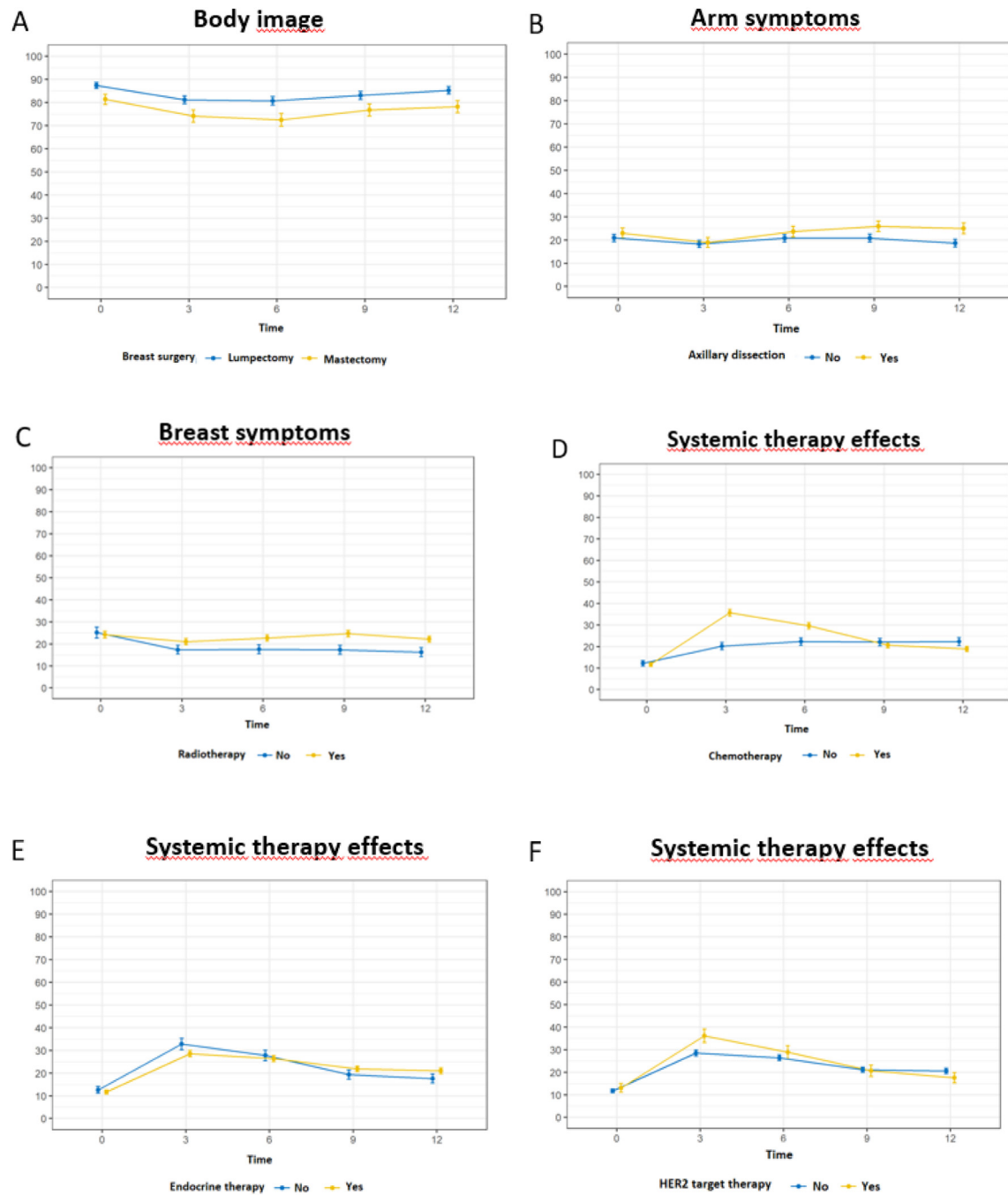


Fig 4. EORTC-QLQ-BR23 mean scores of the symptom and functional scales over time, according to treatment.

The sequential measurements of QoL over time are the most important tool to evaluate the real impact of treatments on breast cancer patients. Due to the fact that patients from the current cohort were mostly treated with curative intent, worse QoL parameters were observed during the first 3–6 months, compatible with the treatment period with greater side-effects, including chemotherapy and radiotherapy. Therefore, a worsening of symptoms related to systemic therapy is expected. Otherwise, an improvement in the psychological perspective was observed, given the possibility of disease remission or cure,

which was confirmed over time in most of the cases. At baseline, a high proportion of breast-conserving surgery may have contributed to higher QoL scores.

Patients with advanced stage were those with more pronounced improvements in QoL scores, probably due to the benefit of the palliative treatment. Research on the treatments responsible for this improvement is warranted. When triple-negative and HER2-positive subtypes were analysed separately, it was possible to measure the temporary negative impact of chemotherapy on QoL, whereas anti-HER2 therapy improved long-term QoL parameters.

Regarding endocrine therapy, the follow-up may be too short to detect differences. In addition, most patients who do not undergo endocrine therapy upfront, receive chemotherapy in the first year of treatment, which can impact the results. It is important to note that changes in mean scores over time are reported in different ways in clinical trials. As there is no well-established cut-off point in the literature, we reported statistically significant differences between groups over time using the linear mixed model. However, we must consider, for example, that differences smaller than 5 absolute points may be statistically significant but not clinically relevant.

Finally, in this study, it was possible to conclude that systemic chemotherapy is the treatment that most impairs the patient's QoL. Regarding local treatments: breast-conserving surgery improved body image perception, patients undergoing ALND experienced long-term symptoms and radiotherapy enhanced breast symptoms. A better selection of patients for systemic therapy, the indication of more conservative therapies (for example, lumpectomy and sentinel lymph node biopsy) and the use of advanced radiotherapy technology, should be pursued in the upcoming years.

Conclusions

In this large cohort of real-world data, our results showed common facts that are usually observed in clinical practice: patients diagnosed with an advanced stage of breast cancer had worse baseline QoL parameters, treatments with more side-effects, such as chemotherapy, translated into a worsening in patients' perception of health and those who underwent curative treatments improved their QoL over time. This report reinforces the importance of ensuring accessibility to treatments with fewer side-effects and less aggressive surgeries. A description of the main treatments responsible for changes in QoL in metastatic breast cancer patients is warranted in future work.

Author contributions

MRM is the guarantor of integrity of the entire study. MRM, GB, DV, FM, MFG and LHA were responsible for study concepts and design. MRM, NN, JC, MFG and LHA carried out the literature research. MRM, NN, JC, ABKA, GB, LCCL, LS, RA, GP, CL, RC, DV, PMA, TAVF, JPP, FM, MFG and LHA were responsible for the clinical studies. MRM, NN, JC, ABKA, GB, DV, PMA, TAVF, JPP, FM, MFG and LHA were responsible for the data analysis. MRM, NN, JC, ABKA and LHA carried out the statistical analysis. MRM, NN, JC, TAVF, JPP and LHA prepared the manuscript. MRM, NN, JC, ABKA, GB, LCCL, LS, RA, GP, CL, RC, DV, PMA, TAVF, JPP, FM, MFG and LHA edited the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clon.2022.05.015>.

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